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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/673,667 | 09/30/2003 | Gregory D. Sempowski | 1579-861 | 2031 |

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| EXAMINER | |
|---|---|
| XIE, XIAOZHEN | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1646 | |

DATE MAILED: 11/29/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/673,667 | SEMPOWSKI ET AL. | |
| | Examiner | Art Unit | |
| | Xiaozhen Xie | 1646 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *18 September 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-15* is/are pending in the application.

4a) Of the above claim(s) *6-9 and 13-15* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5 and 10-12* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *30 September 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *20060918*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

### *Status of Application, Amendments, And/Or Claims*

The Information Disclosure Statement (IDS) filed 18 September 2006 has been entered in full.

### *Election/Restriction*

Applicant's election with traverse of Group I, claims 1-12, and species election of an antibody, in the reply filed on 18 September 2006 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)). Claims 13-15 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Claims 1-15 are pending. Claims 1-12 are under examination to the extent they read on the elected species.

### *Claim Objections*

Claims 1 and 6-9 are objected to because of the following informalities:

Claim 1 needs a comma after atrophy, i.e. "...thymic atrophy, comprising..."

Claims 6-9 recite non-elected species.

Appropriate correction is required.

### *Claim Rejections - 35 USC § 112*

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-5 and 10-12 are rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are directed to a method of treating or preventing Gram-negative endotoxin-induced thymic atrophy comprising administering to a patient in need thereof an agent that inhibits LIF induction of thymic corticosteroids, wherein said agent is a LIF antagonist that inhibits intrathymic production or function of LIF, or inhibits intracellular or membrane associated events that occur between LIF and a LIF receptor, and wherein said antagonist is an antibody or fragment thereof that inhibits interaction between LIF and a LIF receptor. What applicant has described in the specification are an anti-LIF antibody and a p450 11β-hydroxylase steroidognic enzyme inhibitor, metyrapone, which can inhibit corticosteroid production and subsequently inhibit LIF-induced acute thymus atrophy in mice (see Examples 1 and 2). Applicant has not described the genus of the agent. Applicant describes on pp. 5, last paragraph, that examples of LIF antagonists include antibodies, proteins, peptides, glycoproteins, glycolipids, polysaccharides, nucleic acids and so on. However, there is no teaching regarding the relationship of structure to function, such as the chemical structure of these molecules. Thus, the claims encompass a genus of molecules, which vary

substantially in composition, and could have very different structural and functional characteristics from the molecules that Applicant has disclosed.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making of the claimed product, or any combination thereof. In this case, there is not even identification of any particular portion of the structure that must be conserved. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus.

*Vas-Cath Inc. v. Mahurkar*, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (*See Vas-Cath* at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of peptides, and therefore, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that is part of the invention and reference to a method of isolating it. The compound

itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only an anti-LIF antibody and metyrapone, but not the full scope of the claimed agents, are adequately described in the disclosure.

Claims 1-5 and 10-12 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating Gram-negative endotoxin-induced thymic atrophy comprising administering to a patient in need thereof an anti-LIF antibody, does not reasonably provide enablement for administering any agent that inhibits LIF induction of thymic corticosteroids, nor provide enablement for prophylactic treatment. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The claims are broad in that they require the use of a genus of agent. The recitation of "an agent that inhibits LIF induction of thymic corticosteroids production" or "a LIF antagonist" encompasses a genus of molecules, known or unknown, with a diverse range of structures and functions. The specification discloses an anti-LIF antibody, which can inhibit corticosteroid production and subsequently inhibit LIF-

induced acute thymus atrophy in mice. The specification, however, does not provide any guidance for making or using other agents as broadly claimed. There is no teaching regarding the relationship of structure to function, such as what structure characteristics these molecules need to have so that they can function to inhibit corticosteroid production in vivo. While the prior art describes an anti-TNFα Ab that acts as an LIF antagonist by inhibiting intrathymic production and function, and demonstrates its effect in treating thymus atrophy, it fails to provide compensatory guidance for the genus of the molecules. Since the specification does not define what these molecules will be, one of skill in the art would evaluate all non-exemplified molecule to determine their usefulness in treating thymic atrophy. Thus, undue experimentation would be required for the artisan to make and use the invention as broadly claimed.

In addition, the claims read on prophylactic treatment of Gram-negative endotoxin-induced thymic atrophy. The specification fails to provide guidance as to how the artisan could identify those "at risk of" developing a Gram-negative endotoxin-induced thymic atrophy. There is no limitation on the disease or patient population to be prevented. Since the specification fails to provide guidance as to prophylactic treatment, which would be encompassed by the claims, the skilled artisan could not predictably identify all individuals who might be at risk of developing such disease. The scope of patent protection sought by Applicant as defined by the claims fails to correlate reasonably with the scope of enabling disclosure set forth in the specification.

Due to the large quantity of experimentation necessary to generate the nearly infinite number of agents recited in the claims and screen same for treating or

preventing thymic atrophy, the lack of direction/guidance presented in the specification regarding which structural features are required in order to provide function/activity, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which establishes the unpredictability of structure and function, and the breadth of the claims which fails to recite any structural limitations and to define patient population that need prophylactic treatment, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

### *Claim Rejections - 35 USC § 112 second paragraph*

The following is a quotation of the second paragraph of 35 U.S.C. §112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 10 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 10 recites "said antagonist". There is insufficient antecedent basis for this limitation in the claim.

### *Claim Rejections - 35 USC § 103*

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-5, 10, and 12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wang et al. (J. Immunol., 1994, 152(10):5014-5021), in view of Jansen et al. (J Immunol., 1996, 156:4401-4407), and further in view of Watanobe et al. (Brain Res., 2000, 865:97-101).

Wang teaches a method of treating thymic atrophy in mice by administering an anti-TNFα Ab. Wang teaches that lipopolysaccharide (LPS) of Gram-negative bacteria (*Escherichia coli*) is a major factor in the pathogenesis of Gram-negative septic shock, and that Gram-negative bacteria induces thymic atrophy and thymocyte death in mice (see pp. 5014, see Abstract and Introduction). Wang teaches that injection of an anti-mouse TNFα mAb (3.75 mg/kg; i.v.) before the bacterial challenge completely blocked the sepsis-induced thymocyte apoptosis and thymic atrophy (pp. 5018, right column, 2nd paragraph, and pp. 5020, Table III). Because the antibody was injected intravenously, it was, therefore, administered directly to the thymus (claim 10). Although treating sepsis-induced thymocyte death was conducted in mice, Wang describes that sepsis, as well as its potentially lethal complication, septic shock, is one of the most common causes of mortality in clinical bacteria infections (pp. 5014, see Introduction) (claim 12).

Wang, however, does not teach inhibiting LIF induction of thymic corticosteroids, nor teach that the agent is a LIF antagonist (claim 2) or an LIF or LIF receptor antibody (claim 5), that inhibits intrathymic production or function of LIF (claim 3), and that inhibits intracellular or membrane associated events that occur between LIF and a LIF receptor (claim 4).

Jansen teaches that TNFα is an intermediate factor that leads to the release of LIF in primate sepsis (pp. 4401, see Abstract). Jansen teaches that *E. coli*-induced release of LIF was reduced 6- to 10-fold after pretreatment of baboons with the anti-TNFα mAb. Jansen also teaches that signal transduction of LIF is via membrane protein gp130 (pp. 4401, see Introduction).

Watanobe teaches that adrenocorticotropin (ACTH) secretion, which stimulates corticosteroid production via hypothalamo-pituitary-adrenal (HPA) axis, is induced by LIF, and that administration of LPS to mice induces LIF and LIF receptor mRNA, concordantly with stimulated ACTH secretion (pp. 97, see Introduction). Watanobe teaches that administration of an anti-LIF antibody suppressed bacteria endotoxin-stimulated ACTH secretion in rats (pp. 97, see Abstract).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Wang, with those of Jansen and Watanobe to treat Gram-negative endotoxin-induced thymic atrophy in a human patient by administering an anti-LIF antibody to the patient. One of ordinary skill in the art would have been motivated to combine the teachings, because Wang teaches treating thymic atrophy induced by LPS of Gram-negative bacteria by administering an anti-TNFα Ab, Jansen teaches that TNFα acts as an intermediate factor that leads to the release of LIF in sepsis, and Watanobe teaches that the action of LIF in sepsis is to stimulate ACTH secretion and that administration of an anti-LIF antibody can suppress bacteria endotoxin-stimulated ACTH secretion. Therefore, the combined teachings

provide a reasonable expectation of successfully treating Gram-negative endotoxin-induced thymic atrophy in a patient.

***Conclusion***

NO CLAIM IS ALLOWED.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Xiaozhen Xie, Ph.D whose telephone number is 571-272-5569. The examiner can normally be reached on M-F, 8:30-5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary B. Nickol, Ph.D. can be reached on 571-272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Xiaozhen Xie, Ph.D.
November 17, 2006

Eileen B. O'Hara

EILEEN B. O'HARA
PRIMARY EXAMINER